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Circular Letters:

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A Rationale for Plasma in Poliomyelitis: In a study during the 1948 epidemic of poliomyelitis in Los Angeles, the authors observed that the serum albumin level was frequently lower than normal, and that there seemed to be a correlation between the degree of reduction and the severity of the disease. Because of the importance of serum albumin in maintaining the normal osmotic pressure of blood and of the osmotic pressure in regulating the equilibrium of tissue fluids, and because of the possibility that edema of the cord may contribute to the pathogenesis of the paralysis in poliomyelitis, the suggestion was made that a detailed study be conducted to determine (1) the alterations in serum proteins which occur during the course of the disease, and (2) the effect of intensive administration of plasma on both the serum proteins and the neurologic residual of paralysis.

It is postulated that in poliomyelitis the virus-induced infection itself initiates a local shock syndrome (infectious shock) and causes damage to capillary endothelium, vascular congestion, and anoxia, and consequently leads to the transudation of fluid across the impaired endothelium and into the cord; then slight lowering of the plasma osmotic pressure, caused by increased protein catabolism and disturbed protein synthesis as a systemic manifestation of the disease, leads to a prompt increase in both the degree and the rate at which the local edema of the cord develops.

According to reports in the literature, plasma in moderate amounts has been given in the past to patients with poliomyelitis, with the idea of introducing beneficial immune bodies that may be present in the globulin fraction. In one brief study reported by Barnum and Bower in 1944, large amounts of plasma were administered intravenously with apparently good results.

The authors suggest that the chief therapeutic value of plasma when used in poliomyelitis should be expected to result from the effect of its albumin fraction in reducing cord edema. The results with a group of 76 Los Angeles patients, soon to be reported, are in accord with this hypothesis and indicate that generous amounts (from 600 to 900 ml. daily) are required. (Science, 21 Oct. '49, R. M. Eaton and A. G. Bower)

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Effect of Prolonged Intravenous Administration of Dextrose on Beta Cells of Islets of Langerhans: This is a preliminary report on studies being conducted to determine the function of the beta granules of the islets of Langerhans, with special emphasis on their role in diabetes mellitus. It is well established, on the basis of experimental data, that the beta cells are concerned in the elaboration of insulin. Furthermore, there is evidence that the beta granules are intimately related to insulin. Although the exact factors that stimulate the beta cells to elaborate insulin are not fully known, there is evidence that the level of the

blood sugar is important. Anderson and Long found that no secretion of insulin could be detected by assay of the fluid medium after an isolated pancreas had been perfused with blood low in glucose. When such a perfusion was made with blood containing large amounts of glucose, the perfusate indicated a great increase in secretion of insulin.

Houssay observed that repeated or persistent hyperglycemia is an important factor in injuring the islets. He postulated that the hyperglycemia stimulates the beta cells excessively by inducing hypersecretion; if long continued, this overstimulation leads to functional exhaustion and finally to injury and atrophy of the cells. Administration of sugar or of extracts of the anterior lobe of the pituitary gland or the thyroid gland causes elevation of the blood sugar. Lukens, Dohan and Wolcott expressed the belief that the hyperglycemia induced by anterior pituitary extract was the important factor in damaging the islet cells. They found that if the hyperglycemia caused by injections of anterior pituitary extract in cats was prevented by concomitant administration of phlorhizin or insulin, the diabetes mellitus and lesions of the islets usually resulting from the administration of the anterior pituitary extract did not develop.

In 1936 Jacobs and Colwell maintained normal dogs on 50 percent dextrose for as long as 168 hours, giving intravenously from 0.7 to 4.5 Gm. of dextrose per kilogram of body weight per hour. Death ensued, and the chief abnormalities observed at autopsy were hemorrhages in the pancreas and the pituitary gland with some degenerative changes. However, they did not stain the islets by technics that would demonstrate the beta cell granules. Woerner, with continuous intravenous administration of dextrose, maintained hyperglycemia in guinea pigs and found mitotic activity, decreased granulation and hyperplasia of the beta cells. With higher levels of blood sugar, exhaustion of these cells was seen, manifested by degranulation or degeneration. He used the Lane-Bensley staining procedure, which the authors believe is less satisfactory than the Gomori technic. Gomori, Friedman and Caldwell reported varying degrees of beta cell degranulation when transitory elevation of blood sugar was induced by a single intraperitoneal dose of dextrose; as normoglycemia returned, beta granulation was again observed. They offered the opinion that these histologic changes suggested functional activity of the beta cells, possibly related to the secretion of insulin as a response to the elevation of blood sugar. Recently, Dohan and Lukens reported that diabetes mellitus had apparently been induced in cats with repeated intraperitoneal injections of dextrose; the pancreases showed hydropic changes in the beta cells. However, no mention of the beta granules was made.

Normal dogs were given large amounts of dextrose, varying from 425 to 2,250 Gm. continuously by intravenous injection for as long as 9 days.

After an initial transitory rise in blood sugar, there was a latent period of normoglycemia for from 3 to 7 days until sustained hyperglycemia developed. In

all instances the beta cells of the islets of Langerhans were degranulated. In dog one, given destrose to a total of 1,900 Gm. in 4 days, there was, in addition, hemorrhagic necrosis of the islets. It is postulated that these changes are an indication of functional overstrain or exhaustion of the beta cells. This leads to the premise that the beta granules are related to the production of insulin.

It appears that prolonged hyperglycemia stimulates the beta cells excessively and that the overstrain exhausts the supply of insulin and causes degranulation. The necrosis seen in the islet cells of dog one might have been due to overstimulation but other explanations are possible. It is interesting that except for the initial transitory hyperglycemia within a few hours after the infusion of dextrose was begun, normoglycemia was maintained for from 3 to 7 days before persistent hyperglycemia developed. This might be regarded as a period in which the pancreas and other organs involved in carbohydrate metabolism could still meet the great demands placed on them; however, when this overwork was continued, islet cell exhaustion ultimately developed, and the blood sugar again became elevated. This might be regarded as an eventual decompensation of the ability of the islet cells to produce sufficient insulin, following the latent period in which the pancreas could compensate for the massive doses of dextrose and still maintain the normoglycemic state. Before such decompensation is manifested by hyperglycemia, degranulation occurs, apparently as an indication of pancreatic hyperfunction.

The cause of the hyperglycemia of diabetes mellitus is unknown, but the results of these experiments indicate that persistent hyperglycemia may in turn cause definite damage to the beta cells of the islets of Langerhans. This may be of significance in the management of patients with diabetes mellitus, in whom a prolonged state of relatively poor control of the blood sugar may add to the damage of the beta cells which was present when the diabetes first became manifest. (Arch. Path., Oct. '49, S. S. Barron and D. State)

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A Study of Factors Affecting the Prognosis in Cerebral Vascular Accident: It was decided to study the pattern of behavior manifested in a series of spontaneous acute cerebral vascular accidents, in order to appraise the formulation of prognostic standards. The patients studied were all admitted to the Wisconsin General Hospital. All syndromes due directly to trauma, infection, neoplasia, hemorrhagic blood dyscrasias and congenital anomalies were excluded. The diagnoses were carefully analyzed in accordance with the work of Aring and Merritt to segregate them into groups of hemorrhage, thrombosis, and embolism.

In Table I on the opposite page are enumerated the criteria, derived by Aring and Merritt from a clinico-pathologic study of 245 fatal cases of cerebral vascular accident, as the authors employ them to establish their differential diagnoses.

TABLE 1.—CRITERIA FOR THE DIFFERENTIAL DIAGNOSIS OF CEREBRAL VASCULAR ACCIDENT

Sign	Hemorrhage	Thrombosis	Embolism
Syncope	+++	+	±
Cephalalgia, severe, sudden	+++	+	±
Emesis	+++	++	+
Convulsions	++	+	±
Coma	++	±	+
Bloody spinal fluid	+++	±	±
Raised spinal fluid pressure	+++	±	±
Nuchal rigidity	++	+	±
Signs progressive	++	±	±
Embolic disease	±	±	+++

+++ = Usual
++ = Frequent
+ = Infrequent
± = Rare

Notwithstanding the usual clear-cut differences, distinguishing the types is not always simple. There is no one clinical sign by which the differential diagnosis can be decided. The types may so closely approximate one another and overlap that they are occasionally indistinguishable. In making a diagnosis, Aring and Merritt, and later Levy, stress the necessity of a careful analysis of the history, together with the results of the physical and neurological examinations and of the examination of the cerebrospinal fluid. They indicate that on this basis differentiation is possible in nearly 100 percent of cases. Of the 26 patients who died in the hospital, autopsy permission including examination of the brain was obtained in 12. The autopsy substantiated the diagnosis in 11 of these (92 percent). It was assumed, therefore, that the criteria of Aring and Merritt as the authors used them obviated the diagnostic difficulties in the majority of their own cases. So, on the basis of a rigid selection, 107 cases were finally accepted as examples of primary acute cerebral vascular accident. The significant information concerning age, sex, variation in blood pressure, abnormality of respiration, and cerebrospinal fluid analysis was obtained from the protocols in each case. Because the blood pressure is difficult to evaluate immediately after a cerebral vascular accident, it was decided to use the highest pressure recorded during hospitalization, as has been done by other investigators. No attempt was made to localize the exact site of the cerebral lesion, because in acute cases such as these the lability of neurological signs stultifies the value of anatomical localization. In patients who survived the initial attack, an attempt has been made to determine the occurrence of subsequent accidents, the longevity and the patient's state of health at the time of inquiry. This investigation reveals the subsequent histories of 65.4 percent of those who survived the first cerebral vascular accident, with details sufficient for analysis.

Among the 107 selected cases of cerebral vascular accidents there were 75 cases of hemorrhage, 27 of thrombosis, and 5 of embolism, with an aggregate of 132 separate attacks. Fourteen patients (13 percent) have suffered more than one attack, ranging from one to 5 episodes. There were 26 fatalities in the initial attack, with 81 survivors, of whom 53 were traced adequately. Among those who were traced, 33 are known to be alive at the time of this study. The relative proportions of hemorrhage, thrombosis and embolism in this series are similar to those of Aring and Merritt, although the authors believe that neither set of figures represents the true general incidence. In Courville's series of 15,000 autopsies, there were 569 cases of cerebral thrombosis and 388 cases of cerebral hemorrhage; when these are analyzed so as to exclude cases which are not primary, the ratio is still 497 to 208 in favor of thrombosis. An almost

simultaneous clinical survey of 600 cases by Merritt illustrated an incidence of 66 percent for thrombosis and 21 percent for hemorrhage. Some authors believe that the preponderance of hemorrhage in their autopsy series is because most patients with thrombosis recover to a sufficient extent to leave the hospital. It is the authors' experience (which perhaps may be due to certain geographical peculiarities) that because cases of thromboses are milder, such patients are not sent to the Wisconsin General Hospital, whereas patients with hemorrhage, which is more severe, are.

The majority of cases in the present series occurred between the fourth and seventh decades, with the highest incidence in the sixth. The mean average is 56 years and approximates expectation. There are relatively few cases before 40 years of age; only 12 of the cases fall into the younger categories, with 10 of these in the fourth decade. The type of accident is not peculiar to any age. The examples of embolism, however, are too few to permit inference concerning them and, because the authors have not included cases of cerebral vascular accident secondary to other disease, the representation of embolism may not correspond to the true incidence.

When the instances of cerebral hemorrhage are separated into fatalities and survivals, it emerges that, whereas the number of fatalities rises slightly with age, it is far less than proportionate to the increased incidence of such accidents. The disparity between incidence and mortality percentage is most extreme at the age of greatest occurrence. It is furthermore apparent that the percentage mortality per age group increases as that group deviates from the age group of highest incidence. Such cerebral vascular accidents as occur prior to 40 and later than 60 years are more likely to be fatal than an attack occurring between these ages. That this applies to accidents in children is open to question, because in only 2 of the cases were the patients under 30 years of age.

In the cases of thrombosis in the present series there is an age distribution similar to those with hemorrhage. But the mortality rate on first attack is so low, 2 instances among 27 thromboses (7.5 percent) that the condition is a striking contrast to hemorrhage, in which the mortality was 29.2 percent in the first episode. It is deduced from this that age is not so clearly a factor in deaths from cerebral thrombosis as it is in hemorrhage. Age, which assumes considerable importance in the latter type of accident, is of relatively slight significance in the thrombotic accidents; wherefore the accurate delimination of these 2 types is of the utmost value.

The cases of cerebral hemorrhage after the initial attack were divided into fatalities and recoveries, and the blood pressure readings, both systolic and diastolic, were compared. It becomes apparent that until the systolic pressure is elevated above 190 mm. Hg., and the diastolic rises beyond 140, the mortality percentage is not appreciably affected in relation to blood pressure.

With pressure above these readings a significant augmentation of mortality ensues when such pressures are found subsequent to the accident. Whether systolic or diastolic, is of greater value is still problematic, but from the present series it appears that, as an indicator, the systolic has a slight advantage as compared with the diastolic pressure.

The average blood pressure in the fatal cases was 197/115, and in 75 percent of the fatal cases the pressures were above normal. It is pertinent that, among the fatal cases in which there were normal pressures, 4 patients were affected by severe complicating diseases which significantly contributed to the mortality. With the exclusion of these cases, in the remainder the average systolic pressure was 211 and the diastolic 122. On the other hand, the average pressures for the patients who recovered were 168 systolic and 102 diastolic. By treating the groups comparably and eliminating cases with severe complications, these distinctly lower pressures are not altered. Although the number of deaths by thrombosis following the first attack is too small for significant subdivision, it is noteworthy that the pressures in the 2 fatal cases were normal. On the other hand, the mean average pressures for the entire group of those with thromboses were 174 systolic and 105 diastolic, which figures approximate those found in the cases of cerebral hemorrhage with recovery.

Superficially it would appear that considerable significance might be attached to these figures and that very high blood pressure may be a decisive factor. However, when statistically analyzed by the method of chi squares, the element of chance variation cannot be excluded rigidly. The deviation from the required result after the statistical treatment is small enough, nevertheless, to indicate that a more extended series may substantiate the suggested significance of the difference in pressures between the fatal and nonfatal groups.

Consideration of the repetition of attacks in cerebral vascular accident entails 2 problems. One is that of the expected mortality in each succeeding episode, and the other concerns the probability of a subsequent attack. In cerebral hemorrhage the mortality associated with a first attack is 29.2 percent, with a second, 30 percent, with a third, 50 percent, and with a fourth, 100 percent. The examples of third and fourth attacks are so few that these figures are not significant. But there is no difference between the mortality rates of first and second attacks. It is of further interest that the combined mortalities associated with attacks other than the first represent 11 percent of all those patients surviving the first attack. Because the mortality associated with first and second attacks of hemorrhage is similar, the probability of occurrence of the second attack gains added interest. Ten (18.8 percent) of the survivors of the initial cerebral hemorrhage developed one or more acute attacks. With this low degree of probability for a succeeding event and the same mortality for such an occurrence, the hazard from this direction may be regarded as appreciable but not major. Because the incidence of the second attack was 18.8 percent and the

mortality with such an episode was 30 percent, it may be deduced that the expectation of any survivor that he may die of such an occurrence is a 5.6 percent chance or approximately one in 18. For cerebral thrombosis the mortality after the initial attack is very low, 7.5 percent; subsequent attacks in this series are too infrequent to allow further analysis, although this rarity of recurrence appears contrary to clinical experience in thrombosis.

The average time between first and second attacks of cerebral hemorrhage was 46 months with a wide range of variation. In second episodes with fatality, the interval measured 12 months, whereas in nonfatal second attacks the interval was 76 months. This discrepancy is further substantiated by the fact that the average duration between second and third attacks is 2 months in the fatal ones and 10 and 1/2 months in those with survival. This may indicate that the mortality is inversely proportional to the length of time between attacks of hemorrhage; the sooner the recurrent attack ensues the more likely it is to be fatal. However, this is merely an indication which requires confirmation by a larger series of cases.

Two additional phenomena are found to bear upon prognosis; these are coma and abnormal respiration. Whereas the depth of coma is unrelated to the outcome connected with the cerebral vascular accident, the duration is of considerable importance. In the 22 patients with fatal cerebral hemorrhages, the duration was several hours, and in 4 instances was stretched beyond 2 days. In the patients who recovered, such coma as was observed lasted no longer than 2 hours in any instance. On the other hand, in all except 6 (76.9 percent) of the fatal cases, prolonged periods of abnormal respiration, particularly the Cheyne-Stokes phenomenon were exhibited. The patients who recovered have manifested only transient episodes of abnormal respiration. In the fatal cases in which respiratory abnormality was not present, the period of survival time was 11.6 days, compared with 7.9 for the remainder in which severe symptoms were manifested. Prolonged coma and protracted episodes of abnormal respiration may be said to emphasize gravity in the immediate prognosis. (Am. J. M. Sc., Oct. '49, E. C. Tennent and J. W. Harman)

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Survival After Recent Myocardial Infarction: In this report the results of an analysis of 507 cases of recent myocardial infarction are presented. The purpose of this study was to determine the factors concerned in long term prognosis. It was found that the mortality rate was greatest in the first 2 months and lessened progressively. The mortality rate continued to be high for the first year and then remained fairly steady from the second to the fifth year. By the end of from the fifth to the sixth year, 81 percent of the patients were dead. About one fourth of the patients died in the first 2 months, about one half had died at the end of a year, about two thirds at the end of the third year, and

approximately four fifths at the end of 5 years. Thus, the survival rate varied from 72 percent for the first 2 months and 55 percent for the first year to 16 percent for 5 years.

Of the 52 patients who died after the second month in whom the cause of death was known, 19 percent died of heart failure, 6 percent of pulmonary embolism, 65 percent of a new myocardial infarct and 10 percent of miscellaneous causes. There were no deaths after the first 2 months from cerebral apoplexy or renal insufficiency. The authors conclude, therefore, that a new infarct is hazardous, and, although it may occur at any time during the 5-year period, it is most frequent in the first year of the illness.

Hypertension on admission had no effect on the mortality rate in the first 2 months but caused a slight increase, of questionable significance, in the long term mortality. The presence of known angina pectoris at the time of admission and up to one month preceding admission had no deleterious effect on the immediate mortality in the first 2 months, but the average duration of life of those who died after 2 months was somewhat shortened. The presence of heart failure on admission sharply increased the immediate and over-all mortality rate and noticeably shortened the duration of life of those who died after 2 months. It is obvious that heart failure unfavorably affects the immediate and long term prognosis in recent myocardial infarction.

The presence of diabetes mellitus increased the mortality rate in the first 2 months, as well as the over-all mortality rate; however, the long term mortality rate was not greatly altered. The presence of diabetes led to an earlier death among those who died. The authors conclude that the ill effects of diabetes manifest themselves earlier in the period after infarction and that the later prognosis is no worse than that for the entire group.

When low voltage, sinus tachycardia, heart block, or ectopic rhythm was present in the electrocardiogram on admission, the mortality rate in the first 2 months was definitely increased, but the mortality rate after the first 2 months was not significantly altered in this group. Thus, patients in this group who survived the first 2 months had as good a prognosis as the entire group. The absence of low voltage, heart block, ectopic rhythms, and sinus tachycardia led to a much better immediate prognosis, but the long term prognosis was no better than that in the whole group.

Patients who were symptom-free on admission had an immediate mortality rate little different from that for the entire group, but the long term mortality rate was better. Thus, the over-all mortality rate was less than that for the whole group. The average duration of life of those who died was considerably prolonged. Therefore the authors conclude that those who are asymptomatic on admission have a definitely more favorable outlook after the first 2 months.

The mortality rate for the first 2 months, after the first 2 months, and for the entire period showed that older patients were more adversely affected by myocardial infarction than the younger ones. The immediate mortality rate was greater in women than in men, but after the first 2 months the mortality rate was less for women than for men. However, the over-all mortality rate was higher for women than men. Although the mortality rate in the first 2 months was little affected by the location of the infarct, the mortality rate after the first 2 months was definitely less for infarcts on the lateral wall than for those on the anterior or the posterior wall. Little difference was found in the mortality rate after 2 months between infarcts on the anterior wall and those on the posterior wall. The mortality rate was greater than that for the whole group in those in whom the electrocardiogram was classified as showing an atypical coronary pattern. (Arch. Int. Med., Aug. '49, L. N. Katz et al.)

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Endocrine Treatment in Alcoholism: Alcoholism is a psychobiological disorder of huge proportions; approximately three quarters of a million people in the United States alone are incapacitated by it and at least 2 million others seriously affected. The proportion of a person's life involved and his sensitivity to alcohol appear to be more important than the actual quantity of alcohol consumed or the number of years spent consuming it.

In their work with alcoholic patients, the authors have been impressed by 2 relatively distinct groups whom they have classified separately as a matter of expediency in explaining the basic concepts of this study. The first consisted of a large number, particularly among the younger males, who were asthenic in habitus with soft, smooth faces and little or no chest hair, hypotensive, and not infrequently gynecomastic. All of the alcoholic patients with this constitutional make-up, and most nonalcoholic controls having what the authors consider the same so-called allergic diathesis, revealed the triad of hypoglycemia, low 17-ketosteroids, and low androgens. It became clear to the authors that they were dealing with varying degrees of hypoadrenocorticism and that individuals so constituted or so afflicted usually report a low tolerance to alcohol from the time they first begin its use. These individuals appear to be the most susceptible and the most likely to become alcoholic at an early age. Fortunate for many is their early awareness of sensitivity to alcohol and disciplined avoidance of it.

The second group was comprised of those individuals without pre-existing hypoadrenocorticism who, through alcoholic indulgence for a sufficient period, caused eventual damage to the adrenal cortex and to the other associated glands involved with the metabolism of carbohydrates. Lloyd and Williams showed that there was a decrease in lipoid content of the adrenals in almost all of the bodies of patients with alcoholic cirrhosis examined at autopsy. Selye reported that certain conditioning processes such as worry, grief or other alarming stimulus

together with alcohol will produce hypertrophy of the adrenal cortex and eventually hypoadrenocorticism. Both classes of patients, therefore, though constitutionally different, reveal sooner or later the same type of glandular imbalance. Almost all patients in an acute stage of alcoholic intoxication were found to have a relative lymphocytosis. Recently Thorn and others have shown that adrenocorticotrophic hormone decreases the number of circulating lymphocytes releasing antibodies. This is considered to be further evidence that the adrenal gland is involved with alcohol sensitivity.

In this study of alcoholic patients, hypoglycemia was found universally during the nonalcoholic periods. The average fasting blood sugar level was 60.9 mg. per 100 cc., the range being from 54 mg. to 80 mg. per 100 cc. The glucose tolerance curve characteristically began with a subnormal value, rose rapidly to a moderate hyperglycemic level forming a plateau and then, in about 2 hours, suddenly fell again to a subnormal level. Bowman, Wortis, Orenstein and Goldfarb, studying the effect of glucose on the oxidation of alcohol, found depression of the glucose tolerance curve with improvement after one week's hospitalization of the alcoholic patient. Improvement was attributed to emotional factors plus a dietary regimen correcting the effects of malnutrition. Soffer found that low blood sugar and depleted glycogen stores could be restored to normal by the administration of a potent cortical extract. Britton and Silvette observed also that the administration of adrenal cortical extract would prevent glycogen depletion of the liver in fasting adrenalectomized rats and mice. It is the authors' belief that through this medium of insuring sufficient amounts of adrenal cortical hormone, chronic alcoholism may be controlled.

It is postulated that in alcoholics when the blood sugar falls to a certain low level, a craving for alcohol results. This craving manifests itself in a series of symptoms similar to those of hyperinsulinism. Without the previous association with alcohol and his knowledge that relief of these symptoms would ensue, the patient would probably resort to the ingestion of carbohydrate in some form. The consumption of alcohol produces an initial hyperglycemia but eventually leads to hypoglycemia. Continued drinking further decreases the blood sugar, the liver glycogen stores become depleted, and fatty infiltration of the liver occurs. In this state the liver is unable to detoxify the estrogens and sex changes found in chronic alcoholism result, e.g., gynecomastia, loss of hair and gonadal atrophy. The entire process is reversed by the administration of adrenal cortical hormone which mobilizes glycogen from tissue protein, increases the blood sugar and initiates in the liver a return toward normal functioning. The liver again is able to detoxify the estrogens and probably the aldehydes of the alcohol. In addition to these improved physical and laboratory findings, clinical manifestations of disturbed psychic and neurologic function, epigastric distress, abdominal tenderness in the hepatic region, hepatomegaly and other signs of liver involvement occurring particularly during the acute phase of chronic alcoholism, are relieved. From these clinical and laboratory

observations, together with the satisfactory therapeutic results, it seems reasonable to assume that a state of hypoadrenocorticism exists in these patients either as a latent condition or as one induced by the pathologic effects of alcohol.

The procedure developed for the treatment in acute alcoholic states with or without associated chronic alcoholism consists in the administration intravenously of 30 cc. of adrenal cortical extract in 3 divided doses during the first 24 hours, 20 cc. in 2 doses during the second 24-hour period, then one single injection of from 5 cc. to 10 cc. daily for 3 days. It has not been found necessary in the experience of the authors to give the adrenal cortical hormone more frequently than once in 4 hours the first day, one injection at intervals of from 6 to 8 hours sufficing usually. Hospitalization is necessary often and always desirable but it is seldom necessary to hospitalize patients with even the most severe forms of acute alcoholism beyond the fifth day and a number of patients have been treated successfully with but 3 days of hospitalization. Out-patient treatment is possible and frequently with good results but the patient is less well controlled, his tolerance for alcohol is increased, and without sufficient time to alter his attitudes and feelings, there is further risk of drinking. Following discharge from the hospital, from 2 cc. to 5 cc. of the adrenal cortical hormone are given intramuscularly twice a week for 3 weeks, then at weekly intervals for an indefinite period. There is wide individual variation relative to the duration of the convalescent out-patient treatment program. Both during and following hospitalization patients are given a diet high in fat, moderate in protein and restricted in carbohydrate to prevent sudden changes in the blood sugar concentration. Vitamins were given to approximately half of the patients studied but almost without exception, even when dietary deficiency had been present for a long time or when a high degree of alcoholic neuritis existed, the results of treatment with adrenal cortical extract were the same. Some patients with peripheral neuritis appeared to do better with the extract after vitamin B had been discontinued.

Sedation is usually unnecessary because with the first injection of adrenal cortical extract the patient experiences a pleasant sensation of warmth and relaxation. This is of tremendous psychological significance because of the great tendency of alcoholic patients either to substitute sedatives for or combine them with alcohol. Persistent anorexia, when it occurs, may be controlled with daily subcutaneous injections of from 10 to 15 units of protamine-zinc insulin. When signs of testicular atrophy or feminizing symptoms are evident, testosterone propionate may be administered concomitantly with the adrenal cortical hormone. Likewise, testosterone with or without estrogens may be indicated in certain of the female patients, particularly those in the fourth and fifth decades of life with menopausal symptoms. To complete the psychobiologic approach to successful treatment in alcoholism, arrangements are made for each patient to be interviewed by successful members of Alcoholics Anonymous and he is urged to

identify himself actively with the complete AA program. Specialized psychiatric therapy is reserved for the relatively small group of alcoholic patients suffering major psychopathological disorders.

The following is one of the several case histories presented:

A 41-year-old male was admitted to the hospital with a history of chronic alcoholism for 11 years during which time there were several unsuccessful attempts to cure himself. Shortly before admission he developed abdominal distress, anorexia, nausea, vomiting and diarrhea. There were marked nervousness, tremors, nightmares and visual images of people and animals. Several bolstering drinks were needed to start the day and ameliorate his extreme nervousness, apprehension and excessive perspiration. The liver was tender and palpable 3 fingers' breadth below the costal margin. Blood pressure was 160/94. Blood sugar determination upon admission was 74 mg. per 100 cc. Blood count: hemoglobin, 103 percent; red blood count, 4,800,000; white blood count, 8,400. Differential count: polymorphonuclear neutrophiles, 50 percent; lymphocytes, 45 percent; monocytes, 3 percent; eosinophiles, 2 percent. Urinalysis: albumin, trace; sugar, negative. The 17 ketosteroids and androgens were low (7 mg. and 12 international units, respectively).

Treatment was started immediately with 10 cc. of adrenal cortical extract and 30 minutes later a blood sugar determination revealed 100 mg. per 100 cc. Following this single injection, the patient lost completely his craving for more alcohol. The abdominal pain was lessened considerably and disappeared completely 8 hours later after the second injection. He slept without sedation and without nightmares for the first time in 11 years. The following morning he felt so well that he asked to go home. His jitters, apprehensions, colliquative sweating, and tremors which usually are prominent and distressing symptoms the first day of abstinence were gone. His condition was excellent on the fifth day when a glucose tolerance test was made with these results:

	Time	Blood Sugar	Urine
Fasting	8:50 A.M.	80 mg. per 100 cc.	Negative
First specimen	9:30 A.M.	160 mg. per 100 cc.	Trace
Second specimen	10:30 A.M.	117 mg. per 100 cc.	3 plus
Third specimen	11:30 A.M.	52 mg. per 100 cc.	2 plus
Fourth specimen	12:30 P.M.	71 mg. per 100 cc.	Negative

The patient felt entirely well until the third hour test when the blood sugar dropped precipitously to 52 mg. per 100 cc. He then had severe tremors which subsided following another injection of the adrenal cortical hormone. After his discharge from the hospital on the fifth day he was treated as an out-patient receiving 4 cc. of adrenal cortical extract and 25 mg. of testosterone propionate

twice weekly for 3 weeks, then once weekly for 4 months. Fourteen months have passed without any compulsion to drink and all of the symptoms present at admission have disappeared. There has been a remarkably improved personality change with recovery.

The authors consider that the endocrine approach using adrenal cortical extract in treatment for alcoholism is fully justified by the clinical results observed in the patients to whom it has been applied. Further studies are needed for the investigation of the role not only of the adrenals but of the other endocrine structures as well.

Sample Diet During Treatment

Breakfast: 1/2 cup oatmeal with milk and cream, 2 slices of ham and 2 eggs, 1 medium pat of butter, 1 glass of warm milk.

10:00 A.M.: 1/2 cup orange juice or 1 small peach or 2/3 cup of strawberries or pineapple, or 1 glass of milk.

12:30 P.M.: 1/2 cup rhubarb or spinach or 1 tomato or 2 cups watercress or 1/3 head of lettuce, 1/2 cup of carrots or beets or peas or turnips, 1 peach or 2/3 cup of strawberries or pineapple, 3 ozs. of moderately fat meat, 1 large pat of butter, 1 glass of warm milk.

3:30 P.M.: 1 glass of milk.

6:00 P.M.: 1/2 cup of rhubarb or spinach, or 1 tomato or 2 cups of watercress, cream of pea, asparagus or tomato soup, 1/3 head of lettuce or 1 tomato or 2 cups of celery with mayonnaise, 3 ozs. of meat, 1 pat of butter.

Bedtime: 1 glass of milk.

Candies, cola drinks, or other soft drinks absolutely forbidden. (Geriatrics, Sept.-Oct. '49, J. W. Tintera and H. W. Lovell)

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The Chemical Basis for Adrenergic Blocking Activity in Compounds Related to Dibenamine: The experimental and therapeutic usefulness that would result from the discovery of a relatively nontoxic drug specifically blocking the effects of epinephrine and sympathetic nerve activity has stimulated considerable pharmacological research designed to develop such an agent. An entirely new series of adrenergic blocking agents, the β-haloalkylamines, of which N,N-dibenzyl-β-chloroethylamine (dibenamine) is the prototype, recently has been

reported to act quite specifically to block certain excitatory responses to epinephrine and other sympathomimetic amines and to sympathetic nerve stimulation.

This report deals with certain chemical and pharmacological properties of 113 compounds most of which are related chemically to dibenamine. These have been selected as illustrative examples of a larger series of 218 compounds studied in the same manner. A preliminary report of part of this work was presented in 1946. Since that time studies on a few members of this series in addition to dibenamine have been published by other investigators. Several active compounds were reported inactive because of inadequate testing methods. Most of the compounds studied by others are members or minor variations of the basic series presented in this paper and in all cases their potentialities for producing adrenergic blockade are qualitatively predictable on the basis of the requirements for activity revealed in the present study. The details of synthesis and chemical characterization of these compounds will be presented elsewhere.

It is concluded that the highly specific adrenergic blocking activity of members of the dibenamine series can be adequately explained on the basis of a few specific requirements of chemical structure. To be active a compound must meet the following requirements: (1) it must be a tertiary amine or the quaternary derivative of an active amine, (2) it must include at least one β-haloalkyl group capable of forming an intermediate ethylenimmonium (or vinyl) derivative, (3) it must include an unsaturated ring substituent attached to the amine in such a way as to allow resonance stabilization of the active intermediate, (4) in the case of benzyl derivatives, there must be no substitution on the phenyl ring which tends to be out of the plane of the ring. Compounds meeting these conditions were found to be active, and no compound failing to meet all these requirements could be shown to produce significant dibenamine-type adrenergic blockade.

The very low toxicity of dibenamine and most of its active congeners appears to be due to 3 factors, namely, (1) the presence of only one β-haloalkyl moiety, (2) their low aqueous solubility, and (3) the reduced reactivity of their ethylenimmonium (or vinyl) intermediates as a result of resonance stabilization.

Although the chemical basis for activity outlined in this report cannot be considered as definitive, it has proved most helpful in directing the synthesis of a large number of active compounds and should provide useful direction in the development of new β-haloalkylamine adrenergic blocking agents of experimental and clinical value. It should also serve to focus attention upon the importance of the chemical properties of pharmacologically active agents. (J. Pharmacol. & Exper. Therap., Sept. '49, M. Nickerson and W. S. Gump)

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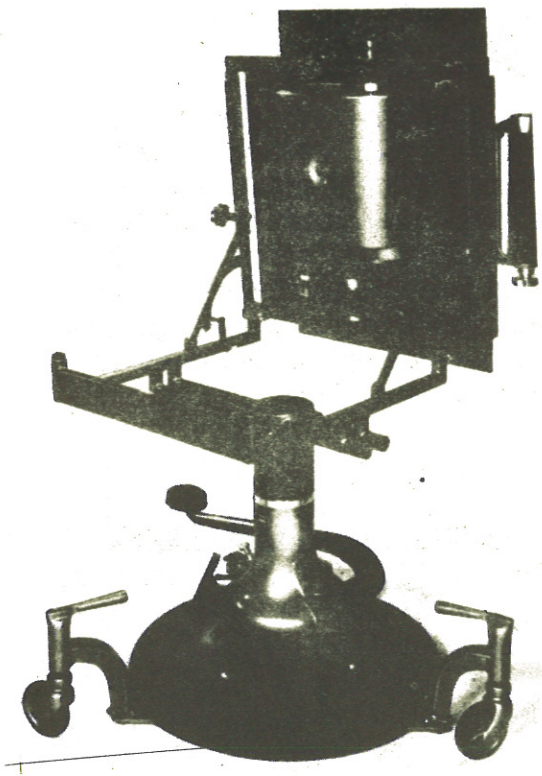
Roll-Film Magazine for Angiography: Charles T. Dotter et al. of the Department of Radiology of the New York Hospital-Cornell Medical Center, New York City, with the cooperation of the Fairchild Camera and Instrument Corporation have devised and employed an automatic roentgen-ray roll-film magazine for angiocardiography and cerebral angiography. This work has paralleled the efforts of Scott in St. Louis who employed a modification of the Fairchild 9-inch aerial camera magazine with a self-cocking high-speed Bucky grid.

The magazine as employed by the authors is mounted upon a motor base plate which in turn is attached semi-permanently to a roentgen-ray table or other suitable support. The magazine is snapped into and out of the base plate for film loading and unloading in the darkroom. An easily removable cover protects 2 film spools, each with a capacity of 75 feet of film 9 and 1/2 inches in width. Two high-speed intensifying screens and a moving parallel grid are mounted on the front of the magazine and sheet lead protects the film supply from undesired exposure. A meter records the total number of films exposed. The magazine is equipped with a handle for easy carrying and weighs only 30 pounds, fully loaded, a weight equivalent to that of three 14- by 17-inch standard cassettes. Loading and unloading is no more complicated than the similar operation on an ordinary roll-film camera. The motor base plate consists of an aluminum plate behind which are mounted a 1/15 horsepower electric motor with reduction gears, and the terminals for connecting electric leads. The outer dimensions of the motor base plate are 23 by 21 and 3/4 inches. With the magazine locked in place, the depth of the entire unit is 8 inches, and the weight is 49 pounds.

When the motor circuit to the magazine is closed from the roentgen-ray control panel the film is advanced 10 inches, then stopped by a clutch mechanism. A pressure plate sandwiches the film between the intensifying screens which are mounted on felt pads and the circuit to the roentgen-ray timer is closed, activating the roentgen-ray exposure. The screens then are separated and the cycle is repeated every 0.5 second as long as motor current is supplied. During motor operation which is continuous, the parallel grid is kept in horizontal oscillation. A stationary fixed focus grid may be substituted for the moving parallel grid and is of particular use during intracranial arteriography.

The authors have employed the roll-film magazine mounted on a Philips pedestal Bucky stand as shown on the opposite page allowing almost unlimited positioning and facilitating vertical or prone angiocardiography, intracranial arteriography, special studies during cardiac catheterization and cardiovascular visualization in the experimental animal. A stretcher may be positioned over the magazine for prone angiocardiography and abdominal aortography. The device has afforded high quality, clearly defined roentgenograms in each application.



The duties of the technician during angiocardiography are simple. The magazine is actuated by a single control button and operation is automatic as long as the switch is held closed. The magazine may be run continuously for an entire cycle of contrast substance through the thorax. It may be run continuously during any selected period or periods of time or single exposures may be made at will. It has been convenient to operate the magazine during the first 3 seconds following the beginning of injection to obtain studies of the right side of the heart with its associated veins and arteries and during the period of opacification of the left side of the heart (between 7 and 10 seconds in the normal individual). At present, a 100 Kv. (peak) rotating anode tube is operated at 200 milliamperes. Exposure of 1/10 second is used at a kilovoltage suited to the projection employed and the size of the patient. In the near future, modifications in timing apparatus now being made will allow 1/60 second exposures at 500 ma. All angiocardiography is done at a 6-foot distance for uniformity and to minimize distortion. Intracranial arteriography and abdominal aortography is performed at a 40-inch distance using a moving fixed-focus grid.

Actual measurements made with an ionization chamber reveal that the patient receives an average total of 4.5 roentgens during a 24-exposure run. The amount of radiation received by the doctor making the injection who is protected by a long apron or a lead screen falls within the allowable limits for such exposure. Calculation of heat units indicates that a run of 24 consecutive exposures during a 12-second period does not exceed the tube limits (rotating anode tube).

Double emulsion roentgen-ray film made by du Pont in 75-foot rolls has proved satisfactory in the authors' experience, as have other standard brands of roentgen-ray films. Recommended time-temperature development is carried out using the Fairchild X-Ray Film developing unit. Following developing, fixing and washing, the film may be conveniently dried as a long strip draped over hangers in the film dryer. The resultant exposed films measure 9 and 3/16 by 9 and 7/16 inches in size. It would be desirable to have a slightly larger film

size than is at present available, but by roentgenoscopy of the patient prior to angiocardiography, satisfactory positioning may be easily obtained.

It is believed that this magazine presents the best available means of angiocardiographic recording and that eventual refinements will be directed along the principles it employs. The unit is commercially available. Other planned applications of the apparatus include uterosalpingography, special studies of gastro-intestinal motor function and electrocardiographically controlled contrast studies of cardiac chamber volume and wall thickness. The small size of the unit will allow the use of 2 tubes and 2 magazines in order to obtain simultaneous recording in 2 projections. Further modes of application are expected to widen the usefulness of this device beyond the scope of this initial preliminary report. (Am. J. Roentgenol., Sept. '49)

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Chloramphenicol in the Treatment in Tsutsugamushi Disease (Scrub Typhus): This report augments information previously published on the first 25 patients with scrub typhus to receive chloramphenicol and the authors' experience is reviewed in the use of this drug in the treatment of a total of 69 persons who contracted tsutsugamushi disease in the vicinity of Kuala Lumpur, Federation of Malaya (see News Letter of 9 September 1949). The results obtained in this group are compared with those observed in 19 patients with the disease who received only supportive therapy and in 3 who were given p-aminobenzoic acid.

Chloramphenicol prepared by the fermentation process was supplied for the current work by Parke, Davis and Company. A small amount of the antibiotic, subsequently administered in capsules, was received as pure crystalline material but almost all of the drug was in the form of tablets containing 0.25 Gm. amounts of active crystalline material. All treatment was by the oral route. The levels of chloramphenicol in the serum and other body fluids were determined by a turbidimetric bioassay method in which the amount of drug in a known standard required to produce 50 percent inhibition of growth of Shigella paradysenteriae (Sonne) is compared with the inhibiting capacity of varying dilutions of the unknown material.

Although some of the 69 patients treated with chloramphenicol were desperately ill when therapy was instituted, there were no deaths in this group. The mortality rate among the 19 untreated patients observed during the present work was slightly greater than 5 percent; this agrees well with the figure of 6.7 percent in a series of 164 patients observed by Lewthwaite in Malaya.

About 6.0 Gms. of chloramphenicol orally over a period of 24 hours was employed in the most commonly used therapeutic regimen in the present work.

This was adequate to render patients, who acquired their disease naturally, afebrile within an average of 32 hours irrespective of the time during the course of the disease when the drug was started. These patients convalesced rapidly and had no relapses. In contrast 54 percent of the 37 volunteers who acquired scrub typhus developed relapses; these persons had been exposed for a number of days in hyperendemic areas during chemoprophylactic field trials. It is apparent that the course of therapy given early in the disease to volunteers was not adequate to control permanently the infection in them. However, the recrudescent disease was controlled without difficulty when chloramphenicol was again administered. Additional information is needed before final conclusions can be drawn about the optimal therapeutic regimen. In the meantime, it is recommended that all patients with scrub typhus, irrespective of the time when treatment is started, be given an initial oral dose of 60 mg. per Kg. of body weight followed by 0.25 Gm. doses of the drug at 3-hour intervals for at least 24 hours. If a recrudescence of fever occurs, the course should be repeated.

Chloramphenicol is of low toxicity for man. No significant untoward effects were observed in any of the 84 patients who received the drug in the current studies. Chloramphenicol appears in the spinal fluid and milk of human beings reaching levels about half those in the blood.

Rickettsemia may occur for short periods before fever begins in tsutsugamushi disease and for a number of hours after treated patients become afebril (J. Clin. Invest., Sept. '49, J. E. Smadel et al.)

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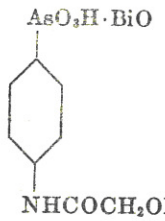
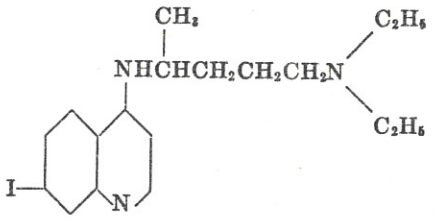
Amebacidal Activity of Bismuthoxy p-N-Glycolyl-Arsanilate and 7-Iodo-4-(1-Methyl-4-Diethylaminobutylamino)Quinoline Diphosphate: The variety of drugs most commonly used for treatment in intestinal amebiasis includes carbarsone, chiniofon, diiodo-oxyquinoline, and emetine bismuth iodide. Emetine hydrochloride is the only drug which has been widely used in the treatment of hepatic amebiasis until the recent reports on the efficacy of chloroquine diphosphate. Because of the marked tendency of patients with intestinal amebiasis to relapse after one or more courses of treatment, many laboratories have continued the search for more effective and less toxic amebacidal agents. This paper presents the results of *in vitro* and *in vivo* screening tests on certain interesting compounds, with special reference to the behavior of bismuthoxy p-N-glycolylarsanilate (Win 1011) and the 7-iodo analog of chloroquine diphosphate (Win 246, also known as SN-7620-5), the formulas for which appear on the following page.

The antiamebic effect of bismuthoxy p-N-glycolylarsanilate was first briefly reported in 1943 by Hauer who called the preparation "WIA." Hauer

WIN 1011



WIN 246



found that WIA was essentially free of toxic properties, was highly effective in clearing stools of Endamoeba histolytica cysts in subacute amebiasis and in carrier states, but was ineffective in hepatic amebiasis and in certain cases in which there was very deep ulceration; he reported that WIA had a distinct anti-diarrheal and sedative effect on intestinal peristalsis in amebic enteritis. This compound has been synthesized in the Chemistry Division of the authors' laboratories and subjected to extensive investigation as Win 1011. It is a bismuth salt of p-glycolylaminophenylarsonic acid, and contains 15.7 percent arsenic and 37 percent bismuth. It is a pure white powder, insoluble in water, and almost tasteless. It has not been possible to establish an acute oral lethal dose of this compound. Rats have tolerated single oral doses of 10 Gm. per Kg. without any apparent toxic effects. In a 21-day subacute toxicity test, Hoppe et al. found that rats tolerated daily doses of 5 Gm. per Kg. per day without discernable toxicity, and 7.5 Gm. per Kg. per day was tolerated with only slight depression of growth rate and without mortality. The drug is well tolerated by human beings at a therapeutic dosage level of 1.5 Gm. per day for from 7 to 12 days when given in divided doses 3 times a day after meals. McChesney has carried out absorption and excretion studies in rats and human volunteers which indicate that only 2 percent of the therapeutic dose is absorbed from the intestinal tract during 10 days of medication. In rats only traces of residual arsenic could be found in the liver, and other tissues were completely free of drug 24 hours after the last dose. No pathological changes attributable to the drug were found. The drug is amebacidal in vitro at a dilution of from 1:30,000 to 1:35,000 when tested against E. histolytica in Hansen's egg infusion medium. All of the evidence accumulated in laboratory studies indicates that Win 1011 is approximately as active and considerably less toxic than other arsenical amebacides currently available. In addition to the clinical trial reported by Hauer, 72 patients have been successfully treated for subacute amebiasis with a complete absence of side effects; of 31 patients who received Win 1011 as the only amebacidal drug, all were promptly cleared of E. histolytica and there were only 3 recurrences with an average follow-up period of 287 days and an average of 10 examinations per patient. In this series one recurrence of E. histolytica was discovered in the fifth week, one in the fourteenth week, and one in the twentieth week after treatment. The desirable properties of high in vitro amebacidal activity, demonstrated in vivo amebacidal activity, low absorption from the gastro-intestinal tract, sufficiently

low toxicity to permit administration of relatively large doses for from 7 to 10 days, and a moderately sedative effect on intestinal peristalsis are attributes of Win 1011 which appear to make it an almost ideal drug for treatment in intestinal amebiasis. An extensive clinical trial and evaluation of Win 1011 is indicated.

The iodine analog of chloroquine diphosphate, namely, 7-iodo-4-(1-methyl-4-diethylaminobutylamino)quinoline diphosphate (Win 246) was synthesized by Dr. A. R. Surrey and was screened as an antimalarial under the code number SN-7620-5. This compound was slightly less effective as an antimalarial than was chloroquine and was not studied extensively until recently. Hoppe and Seppelin have compared the acute toxicity for mice of Win 246 and chloroquine when administered orally and intravenously in aqueous solution. The oral LD_{50} of Win 246 is 810 ± 50 mg. per Kg., as compared with the value of 620 ± 80 mg. per Kg. found for chloroquine diphosphate. The intravenous LD_{50} of Win 246 is 42 ± 2 mg. per Kg. and the LD_{50} of chloroquine diphosphate is 44 ± 3 mg. per Kg. According to Wiselogle Win 246 was found to be 6 times more toxic than quinine as compared with a quinine index of 5 (Q5) for chloroquine. In the authors' laboratories Hoppe and Seppelin found that 18 daily doses of 25 mg. per Kg., administered over a period of 21 days, were tolerated by rats without ill effects or deaths. Drug levels of 50 mg. per Kg. and 100 mg. per Kg., were tolerated without arrest of growth but deaths occurred (3/9 and 3/10, respectively) at those levels; the survivors were autopsied at the end of the test but no pathological changes attributable to the drug were found. Cumulative toxicity was definitely apparent at a dose level of 200 mg. per Kg. The authors have observed degenerative changes in the livers of mice medicated at high dose levels for 3 weeks. Studies on the absorption, tissue concentration, and excretion of Win 246 have not been completed, but it can be inferred from the lower oral toxicity and the greater amebacidal effectiveness in the hamster that Win 246 is absorbed less readily from the intestinal tract than is chloroquine. The production of pathological changes in the liver following repeated high doses is presumptive evidence that Win 246 accumulates in the liver as does chloroquine. It is amebacidal in vitro at a dilution range of from 1:3,000 to 1:7,500 and is slightly more active than chloroquine diphosphate. Both of these compounds, however, are more active than chiniofon or diiodo-oxyquinoline under similar conditions. The circumstantial evidence indicates that Win 246 may be expected to be as active as chloroquine for treatment in hepatic amebiasis and may be more effective for treatment in intestinal amebiasis. Conan has reported clearance of E. histolytica from the stools of 50 percent of patients treated with chloroquine. (Am. J. Trop. Med., Sept. '49, E. W. Dennis et al.)

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Routine Culture Methods in Diagnosing Endamoeba Histolytica: The purpose of this paper is to present data comparing 4 culture methods with the

Heidenhain's iron-hematoxylin stain method in the laboratory diagnosis of amebiasis. This study was undertaken on the request of and with the support of a group of physicians practicing in Memphis, Tennessee.

Stool specimens were collected and brought to the laboratory as soon as possible, most of them arriving within 4 hours after being passed. Smears were made immediately, placed in Schaudinn's fixative, and stained by the iron-hematoxylin method. Fresh saline and iodine preparations were then examined and a portion of the specimen was introduced into culture medium. An effort was made to use 2 or more culture media on each specimen, however, in 117 of 350 specimens only one medium was used. Nelson's egg yolk alcoholic extract medium, St. John's beef heart extract medium, Balamuth's medium special (Difco), and an egg slant overlayed with buffered saline (Shaffer and Frye, 1948) were the media used in this study.

Because the stool specimens were formed, few parasites were observed in the fresh saline or iodine stained preparations. An occasional cyst was found in the iodine preparations. In the more acute cases of amebiasis trophozoites were observed in the saline preparations. Because the authors were interested in finding the chronic cases as well as the acute, the discussion is confined to the results obtained in the culture and iron-hematoxylin stain methods.

Because intestinal protozoan parasites, especially in chronic cases and carriers, are not demonstrable in every stool specimen, each patient was asked to submit 3 stools with a day intervening between specimens. From 145 patients an average of only 2.4 stools per patient was obtained. Of the 145 patients, 97 submitted 3 or more stools, 11 submitted 2 specimens, and 37 submitted only one. Among these 145 patients, 26 (17.9 percent) were found to harbor Endamoeba histolytica. Although 18 of those harboring E. histolytica were discovered on examination of the first specimen submitted, 7 were found from study of the second specimen and one from the third.

In order to find a culture medium suitable for isolation and in which strains of the parasites could be maintained in culture, the 4 media mentioned above seemed to be the most promising with which to start this study. Of the 26 patients found to be positive for E. histolytica, the stools of 25 (17.2 percent of the total patients studied) were positive in culture; 20 (13.8 percent of the total patients studied) were positive by the iron-hematoxylin stain method. Some of the latter had so few parasites that they were revealed only after prolonged study of the stained smear.

Of the 350 specimens obtained from the patients under study, there were 48 specimens which gave a positive culture for E. histolytica although only 28 were found to be positive with the iron-hematoxylin stain method. There were, however, 2 specimens found positive on iron-hematoxylin that were not found to be positive in the culture. There were then, a total of 50 (14.3 percent) of the

350 specimens found positive by using both methods. None of the other culture media revealed the presence of E. histolytica which was not also found to be present in Nelson's medium. Of 7 positive specimens cultured in St. John's medium, only 2 showed any growth. Of 27 positive specimens, only 18 showed any growth in the egg slant, and of 10 positive specimens, 8 grew in Balamuth's medium special. There were 29 of these specimens all of which produced good growth in Nelson's medium.

Nelson's medium proved to be good not only as a diagnostic medium but also as a medium in which to maintain strains of E. histolytica. The authors were able to confirm Nelson's observation that transfers need not be made at frequent intervals. Transfers can be made at intervals of 4 or 5 days or longer, and the strain will continue to grow well. One strain was subcultured after 18 days without noticeable damage to the ability of the organism to reproduce. This strain has since been subcultured 23 times. The authors have carried 13 strains at least 4 passages, one having gone through 36 passages. Amebas other than E. histolytica tend to die out rapidly and will not persist for more than about 2 passages of the culture. This medium was also used for in vitro tests on the amebacidal activity of aureomycin. Another incidental observation was made on 2 stools containing large numbers of E. histolytica cysts. The specimens were kept in the refrigerator, periodically removed and a small amount of feces introduced into Nelson's medium. These cysts remained viable and produced good cultures for up to 21 days in one case and 27 days in the other.

Seven of the 26 patients positive for E. histolytica did not have any other parasite, the remaining 19 had one or more of the other intestinal parasites.

The alcoholic extract cultivation medium is a simple medium to prepare, and it keeps well under refrigeration. Very often a luxuriant growth of amebas is produced in 24 hours even from stools with extremely few parasites. As has been emphasized by Tsuchiya and others the skill of the microscopist is still depended upon for the final identification of the organism. Although final identification in this study was made by use of the polyvinyl alcohol fixative technic of Goldman, in working with the cultures one learns to make a differential diagnosis without the aid of a stain. The data confirms the opinion of others that the use of a good culture medium should be added as a routine procedure in the laboratory diagnosis of E. histolytica. (J. Nat'l Malaria Soc., Sept. '49, R. L. Laird et al.)

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Conversion of the Besler Model 374 Smoke Generator into an Insecticidal Fog Generator: The development of insecticidal fog generators for use in insect control operations has been one of many advancements in this field in the past few years. The equipment is used to supplement other methods and is particularly advantageous in controlling adult mosquitoes and flies. There are limitations to the use of fog generators in that they must be utilized under relatively quiet atmospheric conditions and when the temperature of the ground is less than that of the air. For these reasons ideal conditions are usually encountered in early morning and late afternoon.

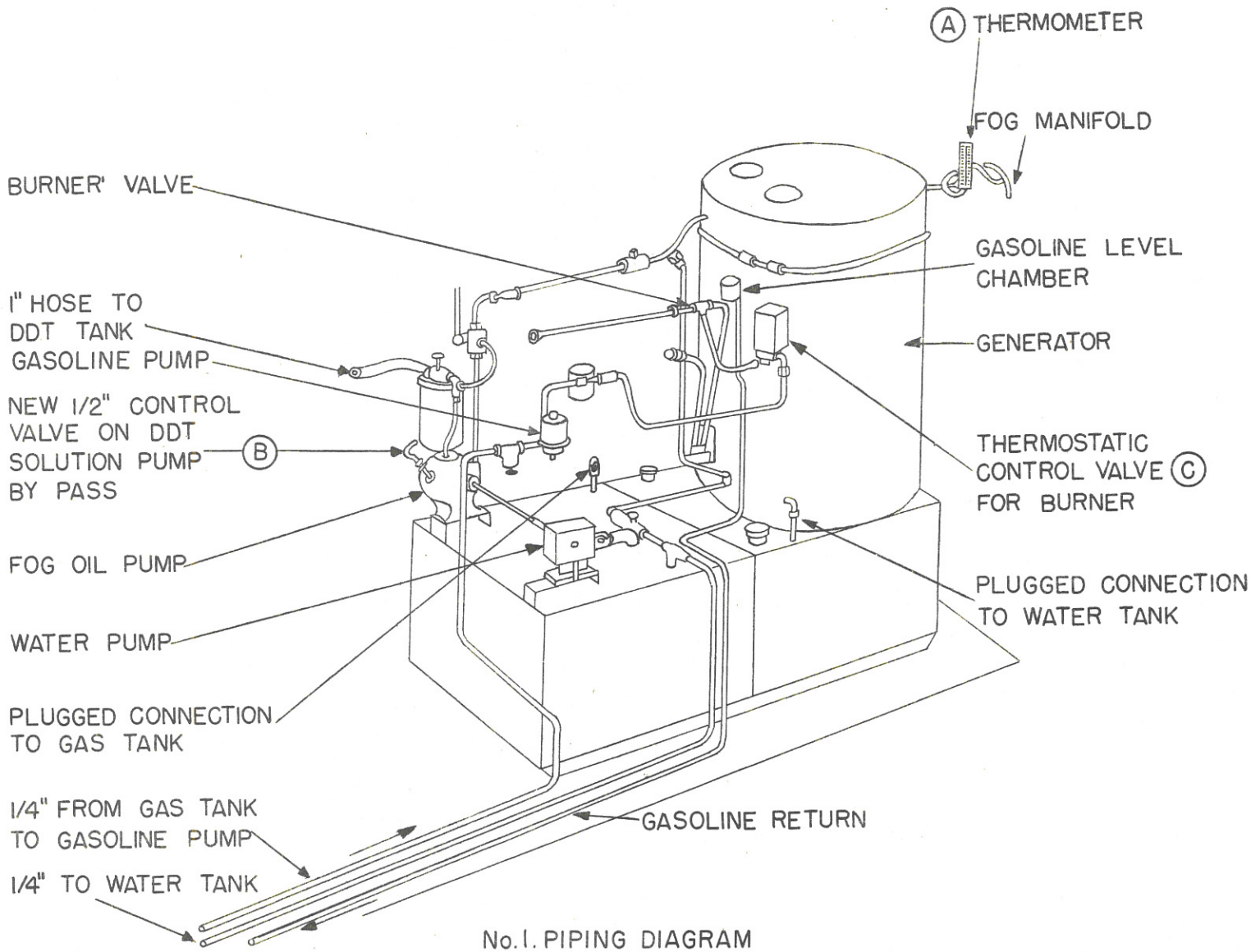
The Mare Island Naval Shipyard, Vallejo, California has converted the Besler Smoke Generator, Model 374 into an insecticidal fog generator by making a few changes in its design. This equipment has proved far superior to the jeep exhaust generator formerly employed by the activity. In order to convert the Besler Model 374 for this purpose a thermometer is placed between the fog nozzle and the generator to determine the temperature of the nozzle (A, diagram 1). Operational temperature of the fog nozzles should be between 450° and 500° Fahrenheit. A one-half inch control valve is installed on the DDT solution pump by-pass to control the amount of solution going to burner (B, diagram 1). A thermostatic control for the burner governs fog nozzle temperature (C, diagram 1). A one-inch gate valve is installed on the DDT tanks to cut off the DDT solution in order to pump water only through coils after operating (A, diagram 2).

Figure 1 shows the converted generator and tanks on a truck in readiness for field use and Figure 2 demonstrates the fog produced when the unit is in operation. Fifty-gallon drums for water and gasoline replace smaller containers built into the smoke generator. The solution used at the Mare Island Naval Shipyard is one part DDT emulsible concentrate (20 percent), one part water, and one part Number 10 or Number 20 nondetergent oil. The oil and concentrate are mixed well by agitation for from 30 to 45 minutes. The water is added with further agitation to give a final concentration of 6 and 2/3 percent DDT. This concentration is the minimum permissible strength required for effective results. It may be necessary to increase the DDT strength to 10 percent in order to achieve the best results.

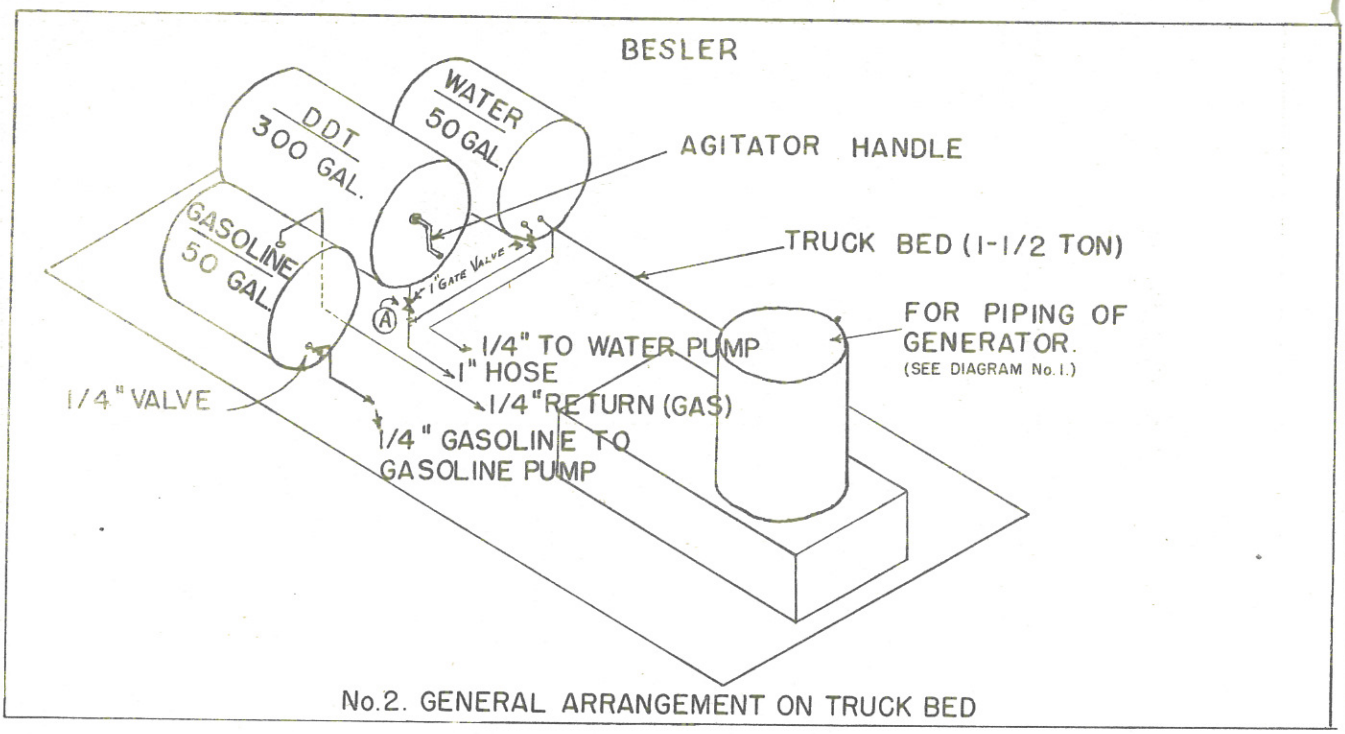
Although this equipment will probably not fully equal commercial generators in efficiency, it should be a valuable supplement to other control equipment with special application to adult mosquito control in the open. It has been noted that because of pump failure intermittent fog discharge occurs quite frequently.

The development of this generator was carried out by Lieutenant (jg) F. R. Colman, MSC, USN, Donal G. Brown, HMC, USN, and William D. Humphrey, Leading Mechanic.

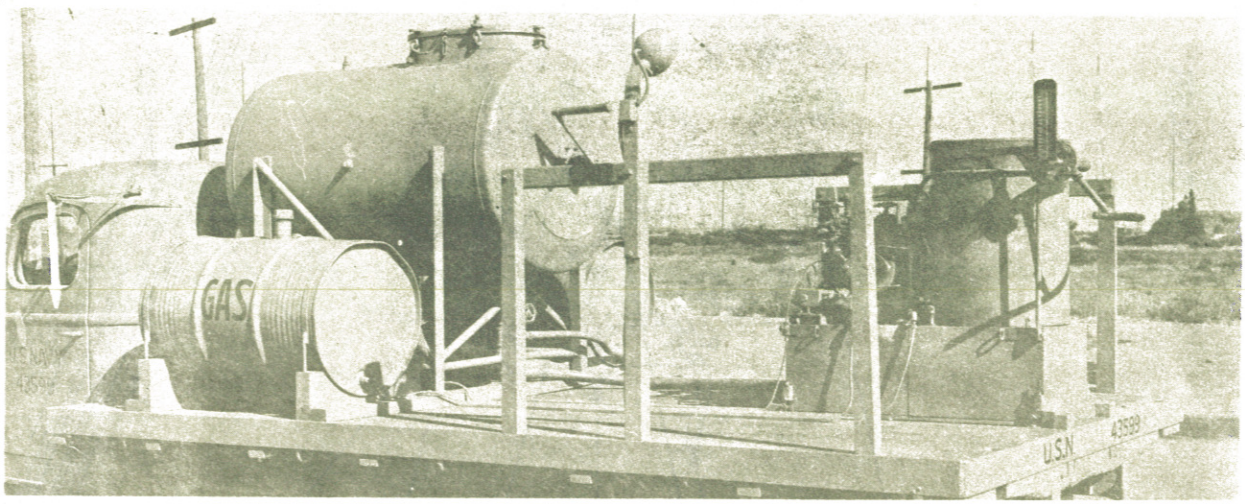
BESLER

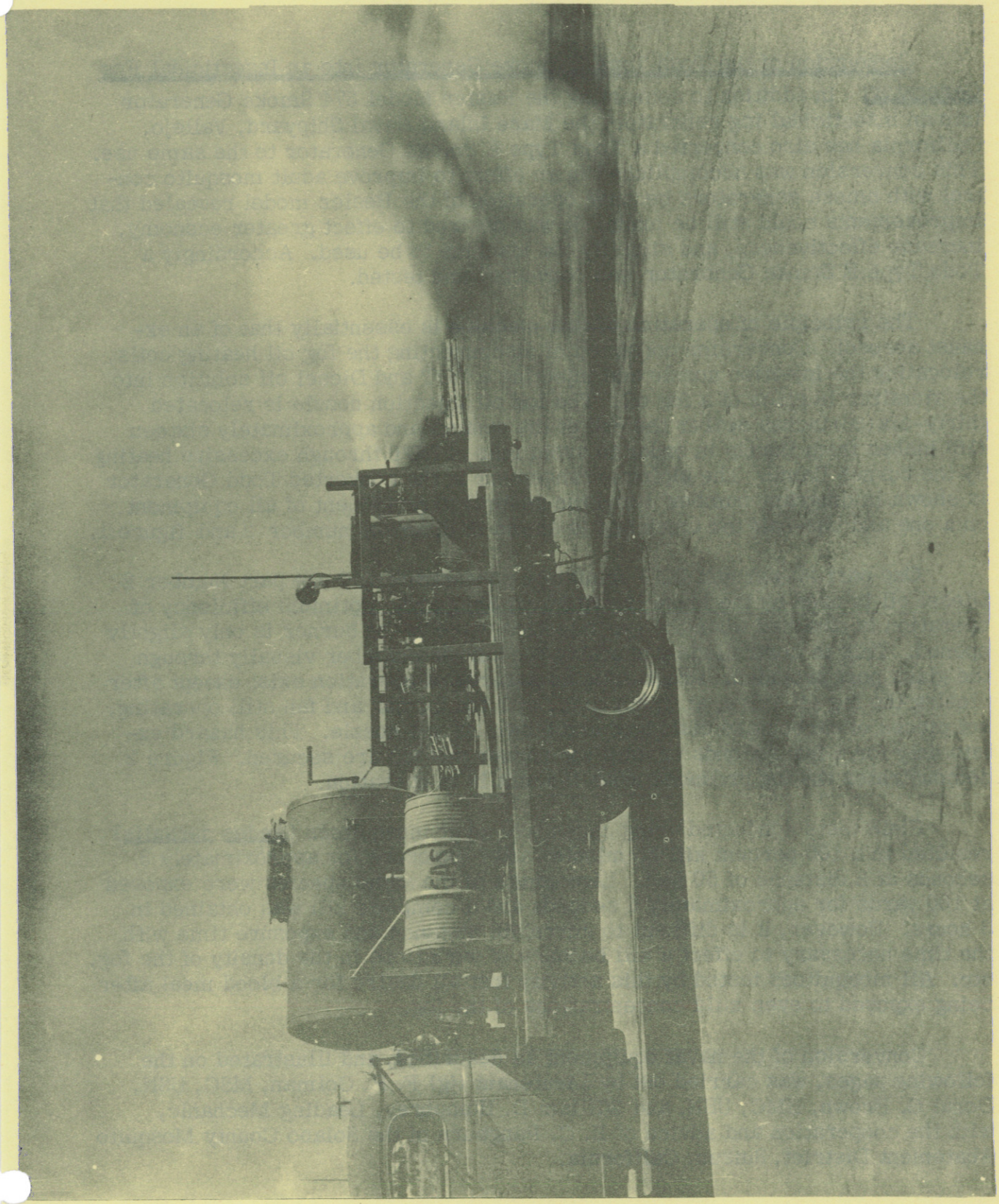


No. 1. PIPING DIAGRAM



No. 2. GENERAL ARRANGEMENT ON TRUCK BED





(Preventive Medicine Div., BuMed)

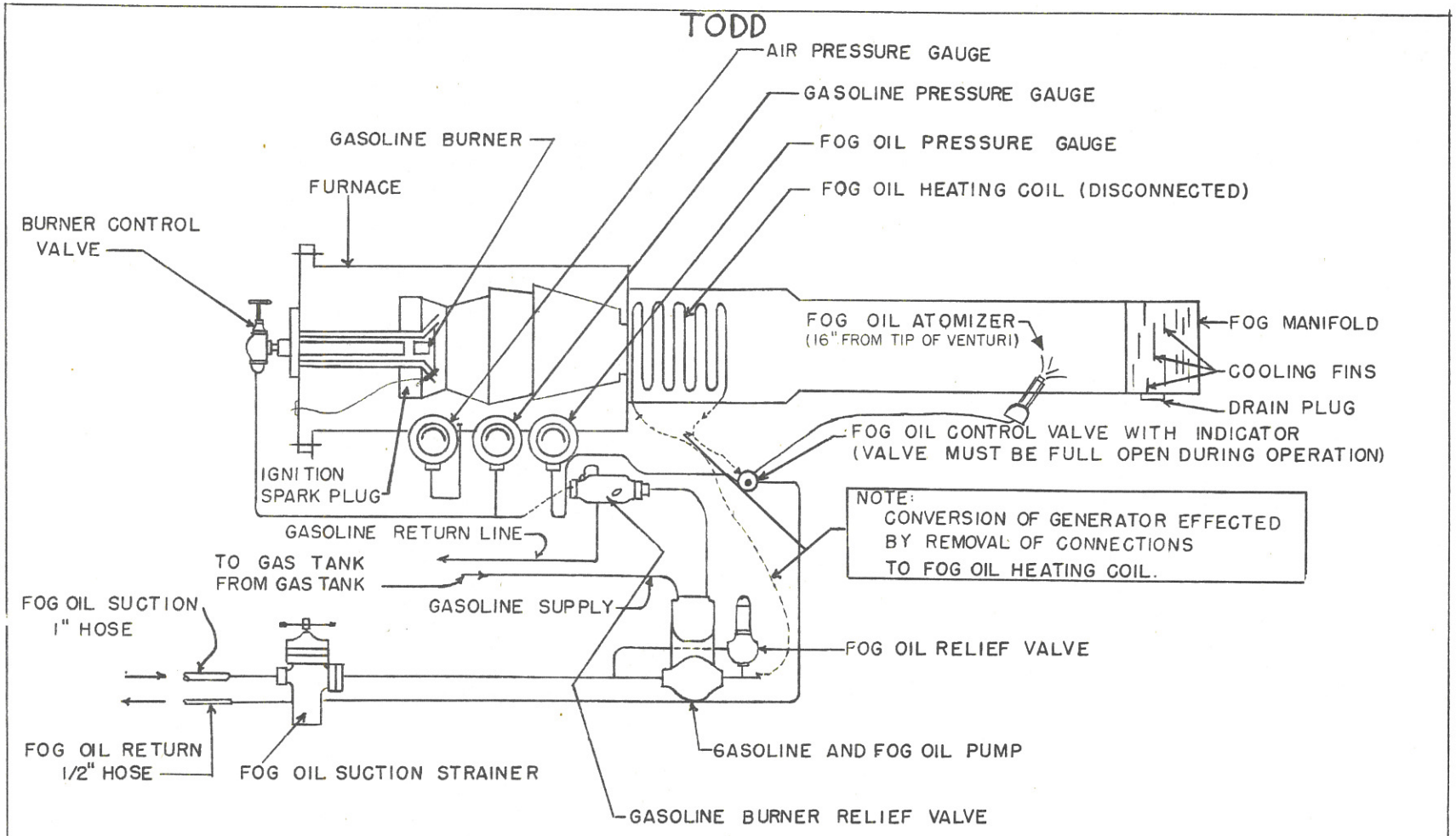
Conversion of the Todd Type E Smoke Generator into an Insecticidal Fog Generator: In addition to converting the Besler Model 374 Smoke Generator into an insecticidal fog generator, the Mare Island Naval Shipyard, Vallejo, California has also converted a Todd Type E Smoke Generator to the same use. This conversion was accomplished in an effort to improve adult mosquito control with smoke generators because operation of the Besler model revealed that improvements could still be made. It was desired to effect greater economy, increase effectiveness, and simplify the machine to be used. Accordingly a Todd Type E Smoke Generator was converted and tested.

The principle of operation of this machine is essentially that of an exhaust aerosol. Conversion consisted of disconnecting the fog oil heating coils, relocating the injection nozzle and injecting a DDT and Diesel oil solution into the atomizer in place of a fog oil. The fog oil injection nozzle is relocated thirty-six(36) inches nearer the end of the venturi and approximately sixteen (16) inches from the tip in order to avoid loss of DDT through excessive heating by the burner flame. The piping arrangement in the converted Todd Generator is shown in diagram number 1 and the general arrangement of all equipment on a one and one-half ton truck bed is shown in diagram number 2 and figure 1.

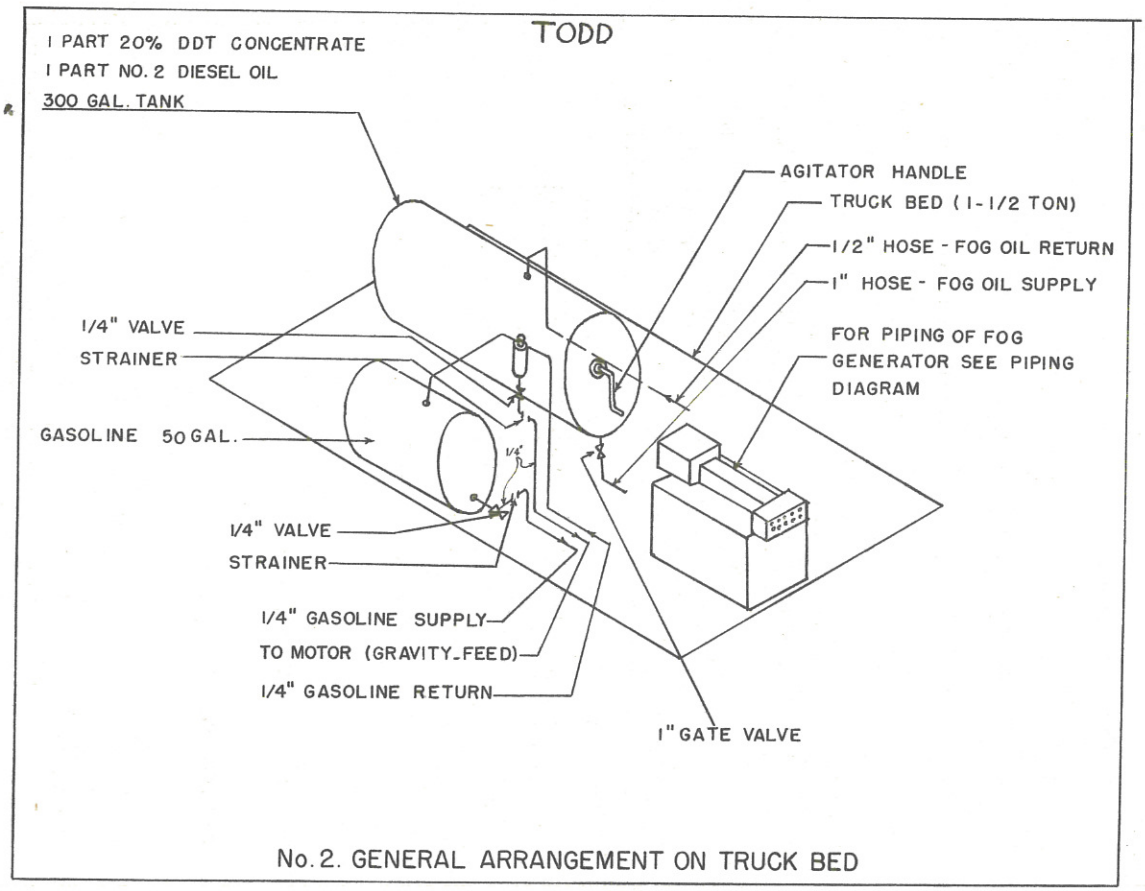
One part 20-percent DDT emulsible concentrate and one part Number 2 Diesel oil is used by the Mare Island Naval Shipyard. Optimum efficiency of operation is obtained when the gas injection valve to the burner is only slightly opened. This is controlled by checking the burner chamber visually through the glass port provided. Practically no hazards of operation exist except after closing the fog oil valve, at which time, with the burner and fan still operating, hot pieces of carbon are dislodged and blown out the nozzle. This hazard exists only for a few seconds or until the burner and fan are secured. Figure 2 demonstrates the fog produced when the unit is in operation.

Field tests conducted using caged live adult mosquitoes (Aedes dorsalis) resulted in a 100 percent kill 35 minutes after exposure for approximately 3 seconds at a distance of 50 feet. Live adults of the same species were exposed at 100 yards for approximately 5 seconds and a complete kill was obtained in 3 hours. However, it is difficult to correlate distance and exposure time with the time necessary to effect a kill because of variations in the density of the fog, etc. All mosquitoes tested by this activity lost all desire for a blood meal after being exposed to even mild concentrations of the fog.

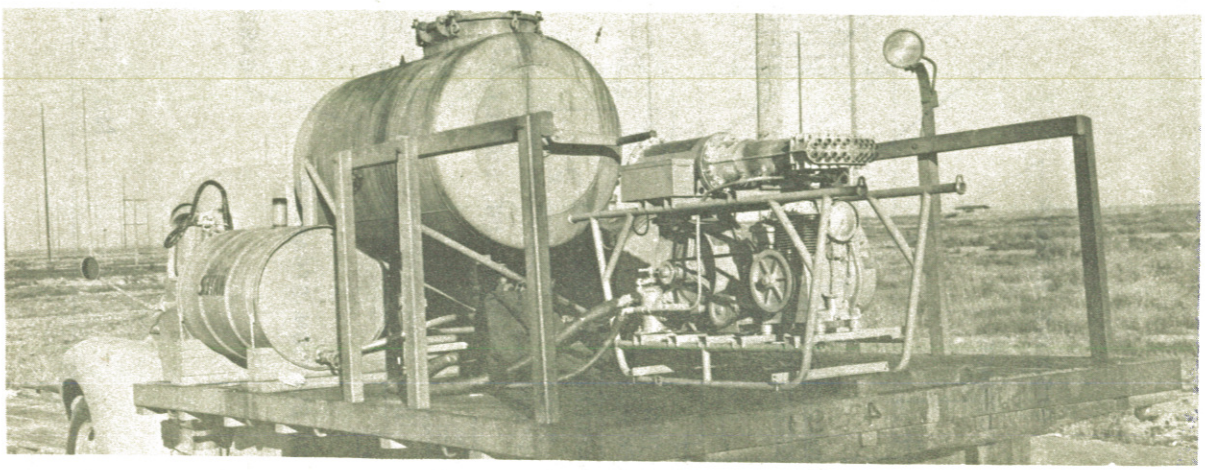
Conversion of the naval equipment as described, and illustrated on the following pages, was carried out by Lieutenant (jg) F. R. Colman, MSC, USN, Donal G. Brown, HMC, USN, and William D. Humphrey, Leading Mechanic, with the cooperation and advice of H. C. Pangburn of the Solano County Mosquito Abatement District, Suisun, California.



No. I. PIPING DIAGRAM



No. 2. GENERAL ARRANGEMENT ON TRUCK BED



(Preventive Medicine Div., BuMed)

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Rehabilitation with Chronic Medical Disease: No matter how poor the prognosis, bedridden patients may become ambulant and fairly active for their remaining years. Disabilities from paralysis, arthritis, and many other ailments are overcome in a 5-point program. Invalids with the average age of 55 were trained after they had been hospitalized for a period of from a few months to 10 years. Of 128 who took the course, 116 achieved from 50 to 100 percent self care and the majority went home.

The service provides physical, occupational, corrective, educational, and manual arts therapy. Walking, stair climbing, speech for the aphasic, social adjustments, and industrial skills are taught, as well as reading, writing, and other academic subjects. Training periods vary from a month and a half for arteriosclerosis obliterans of the legs to 8 months for paraplegia. Strength and coordination improve in patients with multiple sclerosis, hemiplegia, Parkinson's disease, Buerger's disease, heart disorders, asthma, diabetic gangrene, syphilis of the central nervous system, and cirrhosis of the liver. Individual treatment, applied with common sense, perseverance, and ingenuity is required in each case. If a man with bilateral cerebral thrombosis tends to fall backward, high heels may restore balance until natural equilibrium returns.

After discharge out-patient care may be started; when necessary, transportation is provided. Psychiatrist, social worker, and vocational adviser aid the transition to family life and work. (Geriatrics, Sept.-Oct. '49, O. Eisert)

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The Palpatory Examination of the Pancreas: Detection of pancreatic pathology is difficult because of the lack of simple diagnostic procedures.

The author, in 1935, described a palpatory method for examination of the pancreas and a tender point for the body of the pancreas determined by this palpatory method in the dorsal position. He noted the trophic changes of the skin in the epigastrium as a new sign of chronic pancreatitis in 1937. In 1946 and 1947, the author described a second palpatory method in the standing and sitting positions. By comparing the results of the author's methods, in the supine and standing positions, with the method of Mallet-Guy in April 1946, the author noticed that the results, with the patient lying on his right side, are much better if performed by the method which the author elaborated. With the patient lying on his right side, the physician stands in front of him, using his right hand for the examination and employing his left hand on the lower part of the lateral aspect of the patient's thorax. In order to determine if a tender point can be found in the body or tail of the pancreas, or whether the organ is enlarged or not, the examiner palpates deeply with the right hand in the upper part of the mesogastrium and in the left epigastrium, trying to push the movable viscera from left to right to facilitate palpation. The examining hand is pressed deeply until it reaches the left edge of the vertebral column and until the point is reached where the pancreas crosses it, and any tenderness or enlargement of the organ noted. In the second stage of this examination the examiner attempts to palpate the tail of the pancreas by starting in the left hypochondrium, going deeply, and diverting the left rectus muscle to the right, and eventually noting if either tenderness or enlargement is present in the tail of the organ. The essential point here is getting outside the lateral edge of the left rectus muscle. An x-ray check-up by Prof. Misiewicz, after a barium meal, indicated that the stomach and duodenum during such an examination are pushed forward, thus permitting the examining hand to reach the space between the stomach and the vertebral column.

The palpatory method described above lends itself equally well to an examination of the head of the pancreas, merely by placing the patient on his left side. The right mesogastrium is then explored in a similar manner and any enlargement or tenderness in the head of the pancreas ascertained.

The author has employed these methods for nearly 2 years and the results suggest that this easy method is one of great clinical usefulness, because not only is pancreatic enlargement detected, but a tender spot can be located in the head, the body or the tail of the organ. (Am. J. Digest. Dis., Sept. '49, J. W. Grott)

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A Study on Survival of Escherichia coli in Sea Water: Some challenging problems are raised by recent studies of Ketchum, Carey, and Briggs on the viability of Escherichia coli in sea water. These investigations, conducted at the Woods Hole Oceanographic Institute,

have brought out 2 major points. In the first place, the observers have found that, when sewage is discharged into tidal estuaries, the reduction of coliform organisms is much more rapid than that which could be accounted for by dilution (the dilution being measured by changes in salinity). In the second place, the investigations showed that, when E. coli were inoculated with sea water, they died off at a reasonably rapid rate, over a tenth of the initial population disappearing in each 24 hours so that in a week the number left was infinitesimal. When the sea water was boiled, the same result was observed. The striking new fact was disclosed, however, that, when the sea water, instead of being boiled, was autoclaved for from 10 to 15 minutes, the rate of reduction was slowed down to one twentieth of its normal rate, so that the first 10 percent reduction was apparent only after 20 days. The authors are inclined to attribute this phenomenon to the presence of antibiotic or other antibacterial substances which are destroyed by autoclaving but not by boiling. It would seem equally plausible to assume that the mortality of E. coli in ordinary sea water is caused by a lack of necessary foodstuffs (rather than to toxic effects); and that the process of autoclaving produces split products which enable the coliform bacteria to maintain themselves more efficiently. (Am. J. Pub. Health, Oct. '49, Editorial)

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Naval Medical Research Unit No. 4 to do Streptococcus Grouping and Typing: Naval Medical Research Unit No. 4 has been designated as the Streptococcus Grouping and Typing Laboratory for the naval service and all requests for such service are to be directed to this activity.

Because of limited supplies of typing sera available, it is of paramount importance that requests for this service be limited to those situations in which knowledge of the group and type of beta-hemolytic streptococcus is of diagnostic or epidemiologic significance. Normally, this would include such situations as food or milk borne epidemics, outbreaks of scarlet fever, septic sore throat, or epidemiologic surveys. This laboratory is also prepared to determine the antibiotic or sulfa resistance of various strains of streptococci when such information is required.

Requests should be in letter form to the Medical Officer in Charge, Naval Medical Research Unit No. 4, Administrative Command, USNTC, Great Lakes, Illinois and should include such information as the name of the patient, diagnosis and duration of the disease, source of the culture, use of sulfa or antibiotics prior to culture, and the reason information is desired.

Beta-hemolytic colonies, preferably in the matt phase, should be transferred to 5 percent blood agar slants, pH from 7.4 to 7.5 and incubated at 37° C. overnight prior to shipment. Shipment in mailing containers via air mail should be planned for arrival at NMRU No. 4 during the first 4 days of the week. (Preventive Medicine Div., BuMed)

BUMED CIRCULAR LETTER 49-140 28 October 1949

From: Chief, Bureau of Medicine and Surgery
To: All Ships and Stations

Subj: Accounting Instructions; Medical Department Equipment Reclassified as Supplies

Ref: (a) BuMed CirLtr 46-143; AS&SL Jul-Dec 1946, 46-1934, p. 210
(b) BuMed CirLtr 46-144 to NavHosps (Cont.) plus Aiea, Guantanamo Bay and Coco Solo
(c) BuMed CirLtr 47-39; AS&SL Jan-Jun 1947, 47-316, p. 260
(d) BuMed CirLtr 48-52; AS&SL Jan-Jun 1948, 48-339, p. 162
(e) BuMed CirLtr 48-94; to all Shore Sta. (less Hosps) having Med and/or DenDept property
(f) BuMed CirLtr 48-111, N.D. Bul. of 15 Oct 1948, 48-777
(g) BuMed CirLtr 49-141

Encl: (1) List of medical and dental items to be retained as equipment

It is stated in this letter that a thorough study of methods employed by the Bureau of Medicine and Surgery in the classification of all material used by the Medical Department concerning expendability indicates the desirability of paralleling the methods of other bureaus of the Navy Department, and accordingly, as of 1 January 1950, only those catalog items listed on enclosure (1), and similar nonstandard items shall be carried as equipment. Full accounting instructions to accomplish this reclassification are contained in this letter, a full copy of which appears in the 31 October Navy Department Bulletin.

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BUMED CIRCULAR LETTER 49-141 28 October 1949

From: Chief, Bureau of Medicine and Surgery
To: All Ships and Stations

Subj: Plant Account Instructions for BuMed Equipment Reclassified as Supplies

Refs: (a) SecNav ltr M625/ERC:hkc ser 138 of 19 May 1946
(b) SecNav ltr M625/RPH:mm ser 281 of 26 Aug 1946
(c) BuSandA Manual, Volume VI, Chapter 3
(d) BuMed CirLtr 46-166 to all NavStas and MarCorps Activities
(e) BuMed CirLtr 49-140
(f) BuMed CirLtr 48-52; AS&SL Jan-Jun 1948, 48-339, p. 162

It is stated in this letter that in accordance with references all items of equipment reclassified as supplies in accordance with instructions contained in Circular Letter 49-140 shall be removed from Plant Account records in accordance with the procedures as set forth in this letter, a copy of which appears in the 31 October Navy Department Bulletin.

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BUMED CIRCULAR LETTER 49-142 3 November 1949

From: Chief, Bureau of Medicine and Surgery
To: All Medical Department Personnel

Subj: Laboratory Specimens; Instructions for Shipment of in U. S. Mails

Encl: (1) Paragraph 35.17, Postal Laws and Regulations - 1948

1. The instructions relative to the wrapping and packing of laboratory specimens for shipment in the United States mails are enclosed. These regulations are being furnished in order that they will be more readily available to all personnel concerned. C. A. Swanson

Enclosure (1)

U. S. POSTAL LAWS AND REGULATIONS - 1948

Paragraph 35.17

A - DISEASED TISSUES AND OTHER SPECIMENS.

(1) When mailable - Conditions.

Specimens of diseased tissues, blood, serum, and cultures of pathogenic micro-organisms may be admitted to the mail for transmission to United States, State, municipal, or other laboratories in possession of permits referred to in paragraph B of this section only when enclosed in mailing cases constructed in accordance with this regulation, provided that bacteriologic or unfixed pathologic specimens of plague and cholera shall not be admitted to the mails except when prepared as hereinafter specifically provided.

(2) Pathologic specimens of Plague and Cholera.

Pathologic specimens of plague and cholera which have been immersed for at least 72 hours in four times their volume of 4 percent

formaldehyde gas in water, or other fluid of equal or superior disinfecting power for a period sufficient to fix or harden the central portions of the specimen, may be admitted to the mails if packed in the same manner as herein prescribed for other unfixed pathologic tissues (paragraph C, subparagraphs (1), (2), and (3)).

(3) Cultures and infectious material.

Cultures and infectious material of plague, cholera, anthrax, undulant fever and tularemia may be admitted to the mails if enclosed in stout glass tubes sealed by fusion of the glass and packed in a larger stout glass container with a layer of absorbent cotton soaked in 4 percent formaldehyde surrounding the inner container. The outer glass container shall be closed with a rubber stopper or cork of good quality or by fusion of the glass. This double glass container shall then be packed in accordance with the provisions of paragraph C, subparagraphs (2) and (3).

B - PERMIT FROM POSTMASTER GENERAL BEFORE DELIVERY.

No package containing diseased tissue, blood, serum, or cultures of pathogenic micro-organisms shall be delivered to any representative of any of the said laboratories until a permit shall have first been issued by the Postmaster General, certifying that said laboratory has been found to be entitled, in accordance with the requirements of this regulation, to receive such specimens.

C - SPECIMENS OF SPUTUM OR OTHER INFECTIOUS MATERIALS.

(1) Packing.

Specimens of sputum, feces, pus, unfixed diseased tissue, or other infectious material fluid in nature or shipped with nondisinfecting fluid shall be placed in stout glass containers of suitable size (but not more than 3 inches in diameter) and closed with a metal cover with a rubber, cork, or paraffined paper leakproof washer or with a cork or rubber of good quality or by fusing the glass, provided that large fixed specimens of diseased tissue may be prepared for shipment outside of mail bags when packed in accordance with the provisions of subparagraph (2).

(2) Specifications of container.

The aforesaid glass container shall then be placed in (1) a cylindrical sheet-metal box, with soldered joints, closed by a metal

screw cover, or (2) a paraffin impregnated heavy cardboard container with ends made of metal, or a suitable substitute for metal and/or cardboard. A sleeve type of closure may be employed provided that the overlap is at least one third the length of the cylinder and in any case at least two inches. The closure shall be sealed with tape. Or, (3) a one-piece bored wooden cylinder at least three-sixteenths of an inch thick in its thinnest part with a threaded screw top.

The screw top covers shall be provided with rubber or felt washers and shall be threaded with sufficient screw threads to require at least one and one-half full turns before they will come off.

The vial or test tube in the above containers shall be completely and evenly surrounded by absorbent cotton or other suitable absorbent in quantity sufficient to absorb the contents of the glass container, should it be broken.

(3) Sheet-Metal box to be enclosed.

The sheet-metal box with its contents shall then be enclosed in a closely fitting wooden or papier-mache box or tube, at least three-sixteenths of an inch thick in its thinnest part or in a sheet-metal box or tube of sufficient strength to resist rough handling and support the weight of the mails piled in bags. This tube shall be tightly closed with a screw-top cover with sufficient screw threads to require at least one and one-half full turns before it will come off.

(4) Further provisions for mailing.

Cultures in solid media, blood, serum, spinal fluid, fixed and completely disinfected diseased tissue and infectious materials on swabs shall be transmitted in a stout glass container of suitable size (but not more than 3 inches in diameter) and closed with a metal cover with a rubber, cork, or paraffined paper washer or with a stopper of rubber, paraffined cork, or cotton, the last sealed with paraffin or covered with a tightly fitting rubber cap. The tube shall then be packed in a single wooden or papier-mache cylindrical box or tube, at least three-sixteenths of an inch thick in its thinnest part or in a sheet-metal box or tube, of sufficient strength to resist rough handling and support the weight of the mails piled in bags. The glass container in this box or tube shall be completely and evenly surrounded by absorbent cotton or other suitable absorbent packing material. Cultures in media that are fluid at the ordinary temperature (below 45° C. or 113° F.) may be mailed if packed in

stout glass vials closed by fusing the glass and enclosed as in subparagraphs (2) and (3).

(5) Blood specimens.

Specimens of blood dried on glass microscopic slides for the diagnosis of malaria or typhoid fever by the Widal test or of other conditions shall be sent in any strong mailing case which is not liable to breakage or loss of the specimen in transit.

(6) Large shipments of pathological specimens.

Large pathological specimens of fixed diseased tissue and shipments of large numbers of small specimens may be prepared for shipment outside of mailbags. Small specimens of sputum, blood, serum, spinal fluid, pus, feces, fixed or unfixed diseased tissue or other material fluid in nature or shipped with fluid, forming part of such a shipment shall be placed in stout glass containers as in subparagraph (1) and individually evenly wrapped in absorbent cotton or other suitable absorbent material in sufficient quantity to absorb all the fluid in case of breakage. Large specimens of fixed diseased tissue shall be placed in securely sealed glass containers or in securely closed (hermetically sealed or screw-top or approved patent-top) metal containers with the necessary preservative fluid. The container shall be surrounded by sawdust or other suitable absorbent material to protect against breakage or leakage. Small and large specimens so prepared shall be shipped in a strong securely closed box marked "Fragile--Liquid. This Side Up," or with similar inscription, and be transported outside of mail bags.

D - INDORSEMENT ON PACKAGES.

Upon the outside of every package of diseased tissue, blood, serum, or cultures of pathogenic micro-organisms admitted to the mails shall be written or printed the words "Specimen for bacteriological examination. This package shall be pouched with letter mail." Except that large shipments or specimens prepared under paragraph C, subparagraph (6), shall be marked "Specimen for bacteriologic examination."

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BUMED CIRCULAR LETTER 49-143 4 November 1949

From: Chief, Bureau of Medicine and Surgery
To: All NavHosps and AlStas having a Representative of the Medical Department Aboard

Subj: Membership in American Hospital Association; Information Concerning

1. The Bureau of Medicine and Surgery has been advised that officers of the Medical Department of the Navy who are employed in duties directly connected with the administration of naval hospitals are eligible for personal membership in the American Hospital Association. This type of membership may be procured by making request directly to the Headquarters, American Hospital Association, 18 East Division Street, Chicago 10, Illinois.

2. Membership may be obtained after 1 January 1950 for a sum of five dollars ($5.00). Individual members in good standing will have all the privileges of the Association. This does not, however, include membership in the various state and regional associations. C. A. Swanson

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BUMED CIRCULAR LETTER 49-144 8 November 1949

From: Chief, Bureau of Medicine and Surgery
To: All Ships and Stations

Subj: Publications; Downgrading of

Ref: (a) USN Security Manual for Classified Matter, Articles 4-13 and 4-16(b)

This letter, a copy of which appears in the 15 November Navy Department Bulletin, states that because the need for retaining the original security classification of certain publications which originated in BuMed no longer exists, they are downgraded from restricted to unclassified.

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BUMED CIRCULAR LETTER 49-145 8 November 1949

From: Chief, Bureau of Medicine and Surgery
To: All Ships and Stations

Subj: Publication; Downgrading of

Ref: (a) USN Security Manual for Classified Matter, Articles 4-13 and 4-16 (b)

This letter states that in accordance with reference the original security classification of "A History of United States Naval Aviation Medical Research

During World War II," originated by BuMed is downgraded from confidential to unclassified.

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